## REMARKS

Claims 15-36 are presently pending in this Application. In the instant Amendment, The Specification has been amended to include an "Abstract of the Disclosure" on a separate page, and to provide support for Claims 24-27. These amendments to the Specification have not introduced new matter.

Furthermore, in this Amendment, Claims 16 and 32-36 have been canceled, without prejudice, and Claims 15, 17 and 24-31 have been amended. Support for amended Claims 15, 17 and 24-31 can be found generally throughout the instant Application, and particularly on page 2, lines 33-39; page 3, lines 1-24; page 5; page 6, lines 1-39, and Claims 1-14 as filed.

In addition, the Examiner has acknowledged the instant Application is a continuation of PCT/EP00/01530 filed February 2, 24, 2000, claiming priority under 35 U.S.C. § 119 from German Application No. 19908041.0 filed February 24, 2000, even though the Examiner has not received certified copies of these documents. The Examiner has also acknowledged receipt of the Information Disclosure Statement and Form PTO-1449 filed in this matter with the USPTO on August 23, 2001, and the response to the restriction requirement filed March 23, 2004.

The Examiner has also admitted that Claims 16-20 are free of the prior art of record, and would be allowable if rewritten to overcome the rejections under 35 U.S.C. 112, 2nd paragraph, and to include all of the limitation of the base claim and any intervening Claims. Applicants are grateful for these acknowledgements, and admissions, and respectfully submit that, for reasons set forth *infra*, Claims 16-20 as amended herein should be allowed to issue.

***The Invention is Enabled***

Claims 24-35 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner has asserted the Claims contain subject matter that was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the instant Invention. In particular, the Examiner believes there is no description in the instant Specification for the claimed pharmaceutical preparation, nor for the diagnostic kit comprising insulin analogues and additions selected from the group comprising zinc salts, phenol, m-cresol, glycerol, and other buffer substances as claimed in claims 15, 21, 22, and 23, respectively in Claims 24-27 for pharmaceutical and Claims 34-35 for diagnostic kit, respectively. Moreover, the Examiner has asserted that there is no description in the instant Specification for the claimed method of treating diabetes by administering the pharmaceutical formulations of Claims 24-27, respectively, to a host that has diabetes, as is claimed in Claims 28-31. It is the Examiner's position that the instant Specification demonstrates synthesis of B1, B1'-Sub-[$Sar^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer; B1,B1'-Sub-[$D\text{-}Ala^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer; and B1,B1'-Sub-[$Glu^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer (See, e.g., Examples 1-3 of the specification). The Examiner also believes that Example 4 of the instant Specification demonstrates the biological properties for Examples 1-3 set forth in the instant Specification. In the Examiner's opinion though, there are no pharmaceutical formulations or diagnostic kits comprising the insulin analogues as claimed, nor are there methods for treating diabetes by administering the pharmaceutical formulations of

claims 24-27. The Examiner has also asserted there is no *in vivo* showing for the effectiveness of the insulin analogues as claimed, nor is there a recognized model (identified as useful) being treated according to methods of treating diabetes to a host in the manner claimed in claims 28-31.

These rejections are respectfully traversed. Initially, it is noted that Claims 32-35, directed towards, *inter alia*, diagnostic kits, have been canceled, without prejudice. Hence, the rejection of these Claims is MOOT.

With respect to Claims 28-31 however, which are directed towards methods for treating diabetes, it is respectfully submitted the instant Specification as filed provides adequate written description. On page 1, lines 16-18 of the instant Specification, it is explained:

> Diabetes mellitus is treated by employing insulin and insulin analogues in pharmaceutical preparations. In the most widely used form of therapy, the replacement therapy, insulin is administered subcutaneously.

Moreover, for reasons set forth below, the instant Application as filed fulfills the written description requirement with respect to pharmaceutical preparations comprising an insulin analogue of the present invention. Indeed, the very reason for Applicants to invent an insulin analogue of the present invention, as well as a pharmaceutical preparation of the present invention ***is to treat diabetes***. Thus, in light of the disclosures set forth in the instant Application as filed, it is readily apparent that Applicants knew at the time the instant Application was filed that insulin analogues in pharmaceutical preparations ***such as those of the present invention*** are administered to a subject having diabetes in order to treat the diabetes.

Furthermore, contrary to the Examiner's assertion, Claims 24-27 directed towards pharmaceutical preparations of the instant Invention are also readily supported by the instant

Application as filed, and as amended herein. In particular, page 6, lines 27-29 of the instant Application as filed clearly states:

> The invention further relates to a pharmaceutical comprising such insulin analogues, a process for producing a pharmaceutical for treating diabetes, and a process for preparing the insulin analogues.

Moreover, Claim 10 as ***originally filed*** states:

> A pharmaceutical preparation which comprises an insulin analogue as claimed in one or more of claims 1-9 and additions selected from the group comprising zinc salts, phenol, m-cresol, glycerol and buffer substances.

In the Examiner's rejection of Claims 24-27, which are clearly supported by Claim 10 as originally filed, the Examiner asserted that the term "additions" recited therein should be a "pharmaceutical carrier" because, in the Examiner's opinion, it was unclear what would constitute the undefined substances. It is well established that since the claims and the description were filed at the same time, one can amend the Claims based upon the specification without drawing new-matter rejection, and conversely, one can amend the specification based on the claims as originally filed without drawing a new-matter rejection. Thus, the amendment set forth above to page 6 of the instant Specification clearly is supported by the Claims as filed, and does not introduce new matter into the Specification.

In light of this Amendment, which introduces no new matter, it is respectfully submitted the instant Specification readily complies with the written description requirement regarding Claims 24-27, and this rejection should be withdrawn.

***The Invention is Definite***

Claims 15-20 and 24-36 have been rejected under 35 U.S.C. § 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has asserted the recitation "wherein at least one....", "...in an insulin analogue" in Claim 15 is definite because, in the Examiner's opinion, it is ambiguous as to the term "an analogue" in this part of the Claim because the first two words of Claim 15 are also "An analogue."

In this instant Amendment, Claim 15 has been amended to now recite "wherein at least one...", "...in ***said*** insulin analogue (emphasis added)."

The Examiner has also asserted that the phrase "characterized by" of Claim 16 is indefinite because the Examiner believes it is not clear whether the phrase means the formulation must be identical or not. The Examiner has recommended replacing this phrase with the term "comprising".

In the instant Amendment, Claim 16 has been canceled, without prejudice. However, Claim 15, which has been amended to encompass the subject matter of canceled Claim 16, recites the term "comprising" rather than "characterized by".

In addition, the Examiner has asserted that the phrase "the carboxylic acid group" recited in line 2 of Claim 17 is unclear because, in the Examiner's opinion, there is insufficient sufficient antecedent basis for this phrase in Claim 16, upon which Claim 17 depends.

In response, it is respectfully submitted that the phrase "...wherein X is an amino acid in which the carboxylic group is amidated" is readily clear and definite to one of ordinary skill in the art. It is well known in the art that each amino acid has an "amino" group and "acid" group, which is a carboxylic acid group. Indeed, the very name "amino acid" is derived from the

presence of these two groups. Moreover, Lehninger *et al.*, *Principles of Biochemistry 2nd Edition*, Worth Publishers, New York, NY (1993) specifically states on page 112 that "[a]ll of the 20 amino acids found in proteins have a carboxyl group and an amino group bonded to the same carbon atom (the α carbon)....They differ from each other in their side chains, or R groups, which vary in structure, size, and electric charge, and influence the solubility of amino acids in water...." Thus, the phrase "the carboxylic acid" recited in Claim 17 is readily clear as referring to the "amino acid". Yet, merely to further clarify this term, Claim 17 has been amended to recite the phrase "...wherein X is an amino acid in which the carboxylic group ***of said amino acid*** is amidated (emphasis added)."

The Examiner also believes the term "additions" recited in Claims 24-27 is also indefinite. It is the position of the Examiner that "additions" should be a pharmaceutical carrier because the Examiner believes it is unclear what would constitute the undefined "substances".

Claims 24-27 have been amended so that they no longer recite the term "additions". Rather, they recite the term "pharmaceutical carrier" as per the Examiner's suggestion.

Moreover, the Examiner believes Claims 28-31 are indefinite and vague because of the recitation "comprising administering the pharmaceutical..." because, in the Examiner's opinion, it is not clear what kind of administration the claims refer. The Examiner has also asserted it is unclear what the intended outcome of the "treatment" is suppose to be. In support of this position, the Examiner has queried about the appropriate times and conditions necessary to bring about the unspecified effect of the treatment, and that the mode of administration be recited in the Claims.

In the instant Amendment, Claims 28-31 have been amended to recite that administration is performed "subcutaneously". Support for this amendment can readily be found on page 1, lines 16-18 of the instant Specification, where it is explained:

> Diabetes mellitus is treated by employing insulin and insulin analogues in pharmaceutical preparations. In the most widely used form of therapy, the replacement therapy, insulin is administered ***subcutaneously*** (emphasis added).

Moreover, Applicants respectfully submit that the term "treatment" as used in this claims is readily clear and understandable to one of ordinary skill in this art in light of the instant Specification, On page 1, lines 10-18 of the instant Specification it is explained:

> The proteohormone insulin is produced in the β cells of the islets of Langerhans. Its most important physiological effect includes the reduction in the blood glucose level. Insulin deficiency leads to the complex pathological state of diabetes mellitus (type I) which is characterized by deviant glucose metabolism.
>
> ***Diabetes mellitus is treated by employing insulin and insulin analogues in pharmaceutical preparations. In the most widely used form of therapy, the replacement therapy, insulin is administered subcutaneously.***

(Page 1, lines 10-18 of the instant Specification (emphasis added)).

This passage makes clear that treatment is "replacement therapy", wherein insulin or an analogue thereof is administered to a subject because the subject's Islets of Langerhans produce insufficient amounts of insulin, and the intended outcome is to correct the "deviant glucose metabolism" in the subject. Hence, the Examiner's assertions notwithstanding, it is respectfully submitted that the term "treatment" recited in Claims 28-31 is readily clear to one of ordinary skill in the art.

Furthermore, the Examiner has asserted that Claims 32-35 are (a) incomplete

because they recite a diagnostic kit but are ambiguous as to what part(s) of the kit are needed for the diagnostic function; and (b) are indefinite in the recitation "one or more of the insulin analogues", because the Examiner believes it is not clear how more than one is more included or excluded. The Examiner also has the opinion that Claim 36 is indefinite for failing to recite positive active step(s). In particular, the Examiner notes that Claim 36 recites "obtained", "protected", "reacted" and "isolated", which in the Examiner's opinion, do not represent positive active method steps. In order to overcome this rejection, the Examiner has suggested the Claim be amended to recite positive active steps, e.g. "obtaining", "protecting", "reacting", "isolating". Furthermore, the Examiner also believes Claim 36 is indefinite and vague because of the terms "semisynthesis" and "method of genetic manipulation" recited therein because, in the Examiner's opinion, these terms are not defined in the Specification, and it is not clear what these terms mean. Moreover, the Examiner has asserted that the term "and/or" recited it Claim 36 is indefinite because, in the Examiner's opinion, it is unclear whether it means "and" or "or". The Examiner also believes the term "the reaction mixture" is (a) unclear with respect to components in the mixture and their amounts, and (b) lacks proper antecedent basis.

In the instant Amendment, Claims 32-36 have been canceled, without prejudice. Hence this rejection is MOOT.

For the foregoing reasons, it is respectfully submitted that Claims 15-20 and 24- as amended in the instant Amendment are readily clear and understandable to a skilled artisan, and should be allowed to issue.

***The Invention is Novel***

Claim 15 has been rejected under 35 U.S.C. §102(b) as being anticipated by Deppe *et al.* (Naunyn-Schmiedeberg's Archives of Pharmacology, Vol. 35, No. 2, pp. 213-217, August 1994). The Examiner has asserted that in the right column of page 21, Deppe *et al.* disclose an insulin analog consisting of two insulin monomers covalently linked together via a bridge, wherein the insulin monomer is an animal insulin (rat insulin) present in an insulin analogue and physiologically acceptable salts thereof. Hence, it is the Examiner's opinion that Deppe *et al.* disclose covalently bridged insulin monomers as claimed, and anticipates Claim 15 as drafted.

This rejection is respectfully traversed. Claim 15 has been amended to include a structure of an insulin analogue of the instant Invention, in which each B chain of each insulin monomer contains 25 contiguous amino acid residues, and the residue at position 26 (B26) is chemically modified. In stark contrast, Deppe *et al.* teach insulin analogue dimers having monomers wherein the B chains contain ***29*** contiguous amino acid residues. MPEP 706.02 clearly states that "...for anticipate under 35 U.S.C. 102, the reference must teach ***every aspect of the claimed*** invention either explicitly or impliedly". Since, contrary to the Examiner's belief, Deppe *et al.* clearly do not teach an insulin analogue dimer of the instant Invention, this rejection should be withdrawn.

Furthermore, Claims 21 and 22 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Leyer *et al.* (International Journal of Peptide and Protein Research, Vol. 46, No. 5, pp. 297-405, November 1995). The Examiner has asserted that Layer *et al.* disclose B1, B1'-Sub-[$Sar^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer and B1, B1'-Sub-[$D\text{-}Ala^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer (See e.g., abstract and page 398, right column, first

paragraph) as directed to claims 21-22.

This rejection is respectfully traversed. In this paragraph, Leyer *et al.* specifically state:

> The importance of the native B27-B30 side chains for the insulin-like structure, self-association and receptor binding is studied by analogues with multiple amino acid → glycine substitutions. Simultaneously, the role of the peptide backbone B27-B30 for the structure-function relationships is investigated. In a second approach successive elongation of the ***analogue*** [$Ala^{B26}$]des-(B27-B30)-insulin-B26-amide (rel. binding 273%) with amino acids corresponding to the native sequence B27-30 should show the influence of these residues on the receptor binding with respect to position 26 (emphasis added).

Thus, contrary to the Examiner's assertion, Meyer *et al.* do not teach the insulin analogue ***dimer*** B1, B1'-Sub-[$Ala^{B26}$]des-(B27-B30)-insulin-B26-amide, but rather an analogue of insulin, e.g., [$Ala^{B26}$]des-(B27-B30)-insulin-B26-amide, which, unlike an insulin analogue of the present invention, does not even contain D-Ala. With respect to the sarcosine substituted insulin, Leyer *et al.* explain:

> Finally, the ***derivative*** [$Sar^{B26}$]des-(B27-B30)-insulin-B26-amide is prepared as a contribution to the structure-function studies on backbone-modified insulin analogues. The dependence of the receptor binding on the presence of the amide hydrogen in position B26 is examined (emphasis added).

Hence, contrary the Examiner's there are no teachings on page 298 of Leyer *et al.* to maker insulin analogue ***dimers*** with these two analogues of insulin. Rather, Leyer *et al.* prepared the ***derivative*** [$Ala^{B26}$]des-(B27-B30)-insulin-B26-amide in an effort to evaluate the influence of insulin residues B27-30 on insulin's binding to its receptor, and the ***derivative*** [$Sar^{B26}$]des-(B27-B30)-insulin-B26-amide, as a contribution to the structure-function studies on backbone-modified insulin analogues. Hence, the teachings of Leyer *et al.* clearly do not anticipate the

subject matter of Claims 21-22, and this rejection should be withdrawn.

Furthermore, Claim 36 has been rejected under 35 U.S.C. § 102(b) as being anticipated by the teachings of Schuttler *et al.* (Hoppe-Seyler's Zeistchrift fur Physiologische Chemie, Vol. 363, No. 3, pp. 317-330, March 1982). The Examiner has asserted that Schuttler *et al.* disclose the synthesis of six isomeric insulin dimers, linked through selected amino groups of the monomers by a dicarboxylic acid, wherein the monomers are obtained by enzyme-catalyzed semisynthesis. The monomeric insulin analogues are protected by protective groups and the monomers are isolated and purified by cellulose-acetate electrophoresis (See e.g. pp 317-318) as directed to Claim 36. Hence, it is the Examiner's position that Schuttler *et al.* disclose the preparation of insulin analogues by bridging two optionally protected monomeric molecules with the preactivated dicarboxylic acid in which the monomeric analogues are obtained by enzyme-catalyzed semisynthesis.

In the instant Amendment though, Claim 36 has been canceled, without prejudice. Hence, this rejection is MOOT.

***The Invention is Unobvious***

Claim 23 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Leyer *et al.* taken with Deppe *et al.* The Examiner has asserted that Layer *et al.* teach B1,B1'-Sub-[$Sar^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer and B1,B1'-Sub-[D-$Ala^{B26}$]-des-B27-B30)-insulin-B26-amide insulin dimer. The Examiner has admitted that Leyer *et al.* do not teach B1,B1'-Sub-[$glu^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer. However, the Examiner believes the primary reference on page 402, right column of Leyer *et al.* states that insulin

analogues with multiple amino acid substitutions such as glycine substitutions in the region B27-B30 were chosen to show whether the side chains B27-B30 are important to retain the main-chain conformation and ability of the hormone to self-associate. Thus, it is the Examiner's opinion that this disclosure in Leyer *et al.* would motivate one of ordinary skill in the art to substitute insulin analogues with an amino acid of interest in the region of B27-B30. Furthermore, the Examiner has asserted that Deppe *et al.* disclose insulin derivatives with modifications in the regions B23-B30 were synthesized by trypsin catalyzed coupling reactions of des-(B23-B30)-insulin with synthetic peptides (see e.g. abstract). Moreover, the Examiner believes that Figure 1 of Deppe *et al.* shows that dimers with different lengths of the covalent crosslinkers were studied in order to assess the significance of the crosslinkers. In light of the Examiner's interpretations of the teachings of these two references, it is the Examiner's position that at the time the instant Invention was made, one of ordinary skill in the art would have been motivated to prepare insulin by the introduction of one or a few amino acid substitutions into an equivalent insulin dimer of interest (i.e., substitution of $Glu^{B26}$ instead of $Ala^{B26}$ or $Gly^{B2}$, etc.), absent of sufficient objective factual evidence or unexpected results to the contrary.

This rejection is respectfully traversed. Firstly, as explained above, Leyer *et al.* do not teach the B1,B1'-Sub-[$Sar^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin ***dimer*** and B1,B1'-Sub-[D-$Ala^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin ***dimer***. Rather, for reasons explained above, Leyer *et al.* teach the [$Ala^{B26}$]-des-(B27-B30)-insulin-B26-amide, [$Sar^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin ***analogues***. Furthermore, the alanine analogue utilizes L-alanine and not D-alanine (see p. 298, top right column of Leyer *et al.*). Deppe *et al.* teach insulin

dimerized derivatives, but teach ***nothing*** with respect to the introduction of one or a few amino acid substitutions in insulin to form an analogue for use in a dimerized analogue. Rather, as the Examiner has admitted, Figure 1 of Deppe *et al.* shows that dimers with different length of the covalent crosslinkers were studied in order to assess the significance of the crosslinkers. Hence, contrary to the Examiner's assertions, neither of these references taken alone or combination would motivate a skilled artisan to insert a glycine residue into an insulin analogue to form the dimer B1, B1'-Sub-[$Glu^{B26}$]-des-(B27-B30)-insulin-B26-amide insulin dimer. Indeed, no motivation or suggestion exists in either of these references to combine them as the Examiner has done in making this rejection. Rather, it appears the Examiner has impermissibly utilized hindsight in an unsuccessful attempt to construct the instant Invention from these references. The Examiner cannot rely on hindsight to arrive at a determination of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the Applicant's disclosure." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). In the light of the above, it is respectfully submitted that this rejection be withdrawn, and the Claims be allowed to issue.

***Fees***

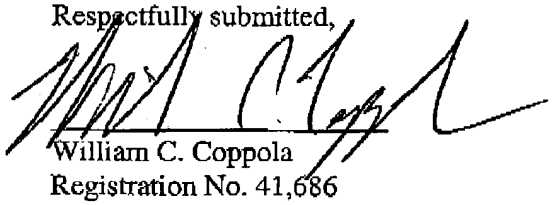
No fees are believed to be necessitated by the instant response. However, should this be

in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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